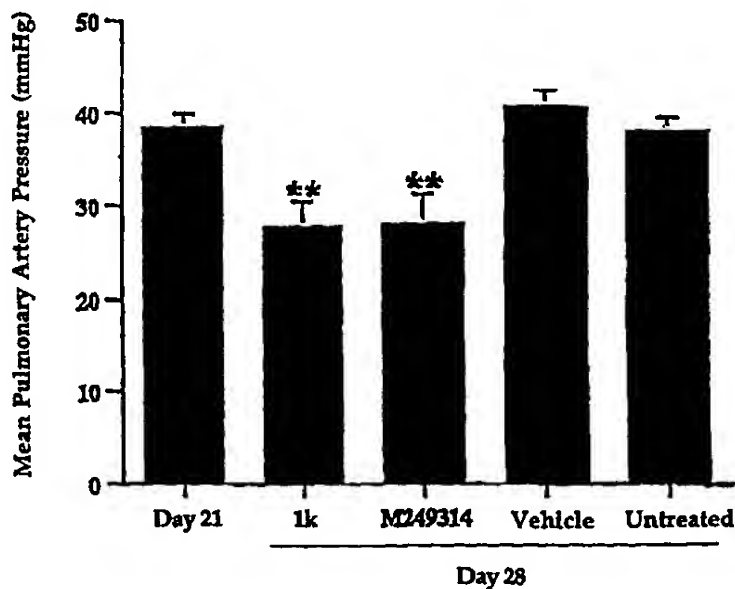




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/IB99/00413 (22) International Filing Date: 26 February 1999 (26.02.99) (30) Priority Data: 60/076,189 27 February 1998 (27.02.98) US (71)(72) Applicant and Inventor: RABINOVITCH, Marlene [CA/CA]; 555 University Avenue, Toronto, Ontario M5G 1X8 (CA). (74) Agent: RUDOLPH, John, R.; Bereskin & Parr, 40th floor, 40 King Street West, Toronto, Ontario M5H 3Y2 (CA).		(81) Designated States: JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published Without international search report and to be republished upon receipt of that report.

(54) Title: TREATING PULMONARY HYPERTENSION THROUGH TENASCIN SUPPRESSION AND ELASTASE INHIBITION



(57) Abstract

A method for treating pulmonary hypertension is described comprising administering an elastase inhibitor to a patient. Inhibition of elastase suppresses tenascin, which leads to a reduction of the smooth muscle cell proliferation associated with pulmonary hypertension.

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TREATING PULMONARY HYPERTENSION THROUGH TENASCIN SUPPRESSION AND ELASTASE INHIBITION

5

BACKGROUND OF THE INVENTION

A variety of therapies have been introduced to try to prevent progression of the pulmonary vascular lesions associated with pulmonary hypertension. Lowering pulmonary artery pressure with vasodilators, such as calcium channel
10 blockers, prostacyclin, and, potentially, nitric oxide therapy, and using anticoagulants to prevent thromboses, are current strategies in use. Recent reports have shown that even in the absences of beneficial acute hemodynamic response, long term prostacyclin has proven effective in a subset of patients for improving symptoms and cardiac output, particularly with exercise. In rare
15 cases, hemodynamic studies show a reduction from systemic to virtually normal levels of pulmonary artery pressure. No patient has, however, been successfully weaned from this therapy and severe rebound effects have been demonstrated upon attempt at withdrawal of prostacyclin. The oral and inhaled prostacyclin analogs may provide as or more effective therapies than intravenous prostacyclin
20 and will certainly be more convenient. In cases where regression has not been achieved, lung transplant appears the only option, and this carries high mortality and morbidity rates in terms of immunosuppressive therapy. Thus, a strategy aimed both at preventing and inducing structural regression of the vascular disease associated with pulmonary hypertension is needed.

25

SUMMARY OF THE INVENTION

The present invention is based upon the discovery that pulmonary hypertension can be treated based upon the suppression of tenascin. Tenascin can be suppressed directly, such as by antisense therapy, or indirectly, by
30 inhibiting serine elastases such as endogenous vascular elastase, a novel enzyme

which has been found to increase tenascin levels, or by inhibiting matrix metalloproteinases which may be activated serine elastases.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

5 In one embodiment, the present invention relates to a method and composition for treating pulmonary hypertension comprising administering to a subject in need thereof, preferably a human being, an inhibitor of elastase, preferably endogenous vascular elastase. Preferably, the inhibitor is a serine elastase inhibitor, such as elafin. Another preferred inhibitor is L-arginine.

10 The term pulmonary hypertension is understood to refer to both primary and secondary pulmonary hypertension.

 The present invention also relates to kits for accomplishing such treatment comprising (i) an effective amount of an inhibitor of elastase, preferably endogenous vascular elastase, (ii) one or more pharmaceutically
15 acceptable carriers and/or additives, and (iii) instructions for use in treating pulmonary hypertension.

 As used herein, the phrase "instructions for use" shall mean any FDA-mandated labelling, instructions, or package inserts that relate to the administration of endogenous vascular elastase inhibitors for the purpose of
20 treating pulmonary hypertension. For example, instructions for use may include, but are not limited to, indications for pulmonary hypertension, identification of specific symptoms of pulmonary hypertension that can be ameliorated by the claimed treatment, and recommended dosage amounts for subjects suffering from pulmonary hypertension.

25 The amount of endogenous vascular elastase inhibitor, which is required in a medication or diagnostic aid according to the invention to achieve the desired effect will depend on a number of factors, in particular the specific application, the nature of the particular compound used, the mode of administration, and the condition of the patient. In general, a daily dose per
30 patient for the treatment of pulmonary hypertension is in the range 25 μ g to 250

mg; typically from 0.5 μ g to 2.5 mg, preferably from 7 μ g to 285 μ g, per day per kilogram bodyweight. For example, an intravenous dose in the range 0.5 μ g to 1.5 mg per kilogram bodyweight per day may conveniently be administered as an infusion of from 0.5 ng to 1.0 μ g per kilogram bodyweight per minute.

5 Infusion fluids suitable for this purpose contain, for example, from 10 ng to 10 μ g per milliliter. Ampoules for injection contain, for example, from 0.1 μ g to 1.0 mg and orally administrable unit dose formulations, such as tablets or capsules, contain, for example, from 0.1 to 100 mg, typically from 1 to 50 mg. For diagnostic purposes, a single unit dose formulation may be administered.

10 In the manufacture of a pharmaceutical composition or kit according to the invention, hereinafter referred to as a "formulation", the endogenous vascular elastase inhibitors are typically admixed with, inter alia, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be
15 deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the inhibitor as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the active inhibitor. One or more inhibitors may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of
20 pharmacy for admixing the components.

In addition to an inhibitor of endogenous vascular elastase, other pharmacologically active substances may be present in the formulations of the present invention which are known to be useful for treating pulmonary hypertension. For example, the inhibitors of the invention may be present in
25 combination with prostacyclin.

The formulations of the invention include those suitable for oral, inhalation (in solid and liquid forms), rectal, topical, buccal (e.g. sub-lingual), parenteral (e.g. subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any given case

will depend on the nature and severity of the condition being treated and on the nature of the particular form of inhibitor which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of inhibitor; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients).

In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising the active compound(s), in a flavored base, usually sucrose and acacia or tragacanth; and pastilles comprising the active compound(s) in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of endogenous vascular elastase inhibitors, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of

subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood. Injectable formulations according to the invention generally contain from 0.1 to 5 % w/v of active compound and are administered at a rate of 0.1 ml/min/kg.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound(s) with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w, for example, from 0.5 to 2% w/w. Formulations for transdermal administration may be delivered by iontophoresis (see, for example, Pharmaceutical Research 3(6), 318, (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound(s). Suitable formulations comprise citrate or bis/tris buffer (pH 6) or ethanol/water and contain from 0.1 to 0.2 M active ingredient(s).

The invention is further illustrated by the following, non-limiting examples.

Increased elastase activity has been demonstrated to play a pivotal role in the pathobiology of pulmonary hypertension in rats with monocrotaline-induced pulmonary vascular disease, as well as in experimental coronary artery neointimal formation where there appears to be a cooperative interaction with cytokines, especially interleukin 1B, in inducing the vascular disease. In addition, increased expression of the matrix glycoprotein tenascin is evident in obstructive pulmonary arteries with extensive neointimal formation as assessed in lung biopsy and in monocrotaline induced pulmonary vascular disease.

An early increase in elastase activity has been shown with the development of the vascular lesions in monocrotaline (Mc)-treated rats and a later increase with progressive disease. A cause and effect relationship is demonstrated in studies in which elastase inhibitors have been used prior to the
5 Mc-induced endothelial injury to prevent the structural changes and associated pulmonary hypertension or, when they have been administered later in the course of the disease to retard its progression.

Subsequent studies related the endogenous vascular elastase (EVE) in the pulmonary arteries of rats with pulmonary hypertension from other etiologies,
10 e.g., hypoxia. Here, an early increase in elastase activity is followed by the development of pulmonary hypertension (PH) but a later increase in elastase does not occur. This model differs from the Mc-induced PH in that it is not progressive and, in fact, will regress upon removal of the rats from the hypoxic environment. Subsequent studies showed that EVE is produced by the smooth
15 muscle cells of the vessel wall and that it appears to be structurally related to the serine proteinase, adipsin.

This mechanism of elastase induction is further supported by *in vitro* studies. Common to all clinical and experimental PH producing stimuli or etiologies is evidence of endothelial perturbation and injury. It is believed that
20 the structural and functional endothelial alterations result in loss of the endothelial barrier function and that, as a result, serum or endothelial factors 'leak' into the subendothelium and stimulate elastase activity in smooth muscle cells. Studies have, in fact, shown that one or more serum factors which appear to include apolipoprotein A1 can stimulate elastase activity by an integrin-
25 mediated event which results in phosphorylation of focal adhesion kinase (FAK) and extracellular related kinase (ERK1/2) which transactivates AML-1, a putative elastase transcription factor. It has also been shown that the endogenous vascular elastase (EVE) releases potent growth factors, such as fibroblast growth factor (FGF)-2, from an inactive form bound to proteoglycans

in the extracellular matrix to a biologically active form which promotes smooth muscle cell proliferation.

This effect is enhanced through the concomitant expression of the matrix glycoprotein tenascin which can be induced by FGF-2 directly or through the elastase-driven upregulation of matrix metalloproteinases. The tenascin serves to alter the smooth muscle cell cytoskeleton and, by clustering the $\alpha v\beta 3$ integrin receptors, also clusters the receptors for growth factors, such as epidermal growth factor (EGF) which rapidly phosphorylate upon addition of the ligand, culminating in a nuclear signal. Cell culture studies have shown that tenascin promotes FGF-2 dependent and is a prerequisite for EGF-dependent SMC proliferation. It has also been shown that the degradation products of elastin, elastin peptides, cooperatively interact with cytokines such as interleukin 1 B in inducing SMC fibronectin production, the latter being a promoter of SMC migration.

It has also been shown that, when SMC are stress-unloaded by floating them in collagen gels, matrix metalloproteinases are downregulated, as is tenascin, and the cells undergo apoptosis or programmed cell death. Tenascin is critical to this process, since its supplementation in the gels will rescue cells. Hypertrophied pulmonary arteries, when placed in floating collagen gels, show regression of the medial thickening to normal values when they are treated with elastase or matrix metalloproteinase inhibitors or tenascin antisense agents. There is a progressive reduction in medial width when the hypertrophied pulmonary arteries are placed in released collagen gels and a progressive increase when placed in restrained collagen gels. This regression appears to be associated with reduced tenascin expression and apoptosis.

In vivo induction of pulmonary hypertension with serine elastase inhibitors in experimental rats.

Pulmonary artery pressure was monitored in groups of rats (n=6) at 21 and 28 days after injection with monocrotaline. Rats were given either the

orally bioavailable serine elastase inhibitor 1k or related compound M249314 (both from Zeneca) twice daily by gavage between 21 and 28 days. Control groups of rats were given vehicle between 21 and 28 days instead of inhibitor. As shown in Figure 1 (in vivo administration of serine
5 elastase inhibitors reverse progressive increases in pulmonary artery pressure following monocrotaline injection into the rat), orally bioavailable highly selective serine elastase inhibitors produce a significant reduction in the levels of pulmonary artery pressure when comparing values in the control and untreated rats. This clearly shows that the orally
10 bioavailable inhibitors given for 7 days are highly effective in inducing regression of pulmonary hypertension.

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art
15 that various changes and modifications can be made therein without departing from the spirit and scope of the invention.

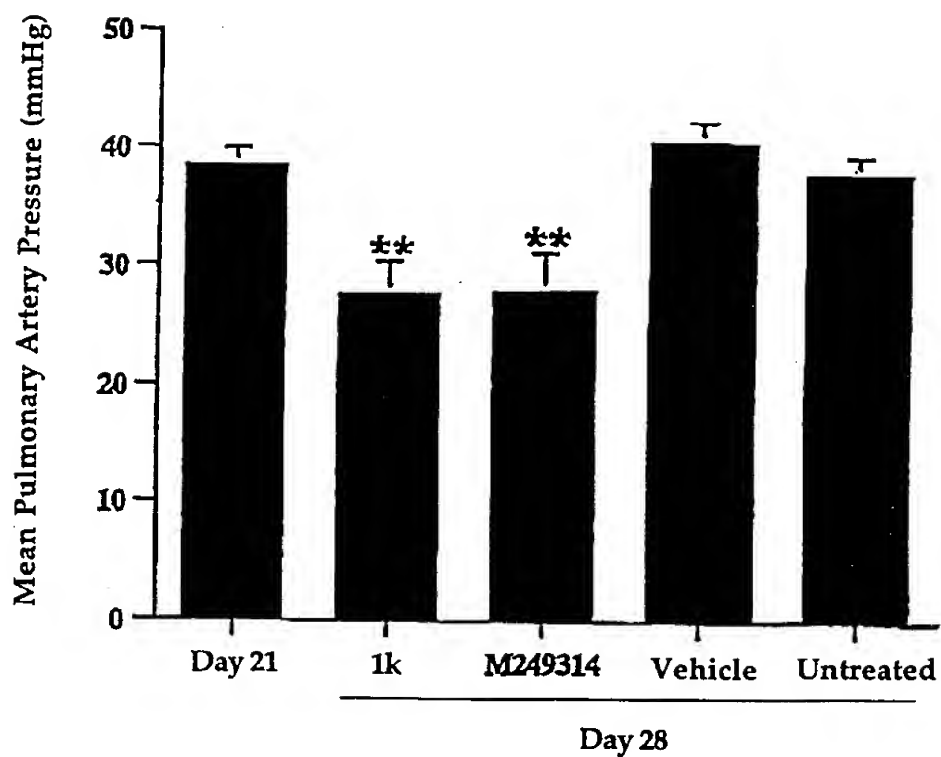
WHAT IS CLAIMED IS:

1. A method for treating pulmonary hypertension comprising administering to a subject in need thereof an effective amount of an inhibitor of elastase.
2. The method as claimed in claim 1 wherein the subject is a human being.
3. The method as claimed in claim 1 wherein the inhibitor is a serine elastase inhibitor.
4. The method as claimed in claim 1 wherein the inhibitor is elafin.
5. The method as claimed in claim 1 wherein the inhibitor is L-arginine.
6. The method as claimed in claim 1 wherein the subject suffers from primary pulmonary hypertension.
7. The method as claimed in claim 1 wherein the subject suffers from secondary pulmonary hypertension.
8. A method for treating pulmonary hypertension comprising administering to a subject in need thereof an effective amount of an agent to suppress tenascin.
9. The method as claimed in claim 8 wherein the subject is a human being.
10. The method as claimed in claim 8 wherein the agent to suppress tenascin is a serine elastase inhibitor.
11. The method as claimed in claim 10 wherein the inhibitor is elafin.

12. The method as claimed in claim 8 wherein the agent to suppress tenascin is L-arginine.
13. The method as claimed in claim 8 wherein the subject suffers from primary pulmonary hypertension.
14. The method as claimed in claim 8 wherein the subject suffers from secondary pulmonary hypertension.
15. A kit for treating pulmonary hypertension comprising (i) an effective amount of an inhibitor of elastase, (ii) one or more pharmaceutically acceptable carriers and/or additives, and (iii) instructions for use in treating pulmonary hypertension.
16. A kit for treating pulmonary hypertension comprising (i) an effective amount of an agent to suppress tenascin, (ii) one or more pharmaceutically acceptable carriers and/or additives, and (iii) instructions for use in treating pulmonary hypertension.

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FIGURE 1



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(21) International Application Number: PCT/IB99/00413 (22) International Filing Date: 26 February 1999 (26.02.99) (30) Priority Data: 60/076,189 27 February 1998 (27.02.98) US (71)(72) Applicant and Inventor: RABINOVITCH, Marlene [CA/CA]; 555 University Avenue, Toronto, Ontario M5G 1X8 (CA). (74) Agent: RUDOLPH, John, R.; Bereskin & Parr, 40th floor, 40 King Street West, Toronto, Ontario M5H 3Y2 (CA).		(81) Designated States: JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 28 October 1999 (28.10.99)
(54) Title: TREATING PULMONARY HYPERTENSION THROUGH TENASCIN SUPPRESSION AND ELASTASE INHIBITION (57) Abstract A method for treating pulmonary hypertension is described comprising administering an elastase inhibitor to a patient. Inhibition of elastase suppresses tenascin, which leads to a reduction of the smooth muscle cell proliferation associated with pulmonary hypertension. More specifically, the tenascin suppressant is L-arginine and the elastase inhibitor is elafin.		

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INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/IB 99/00413

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/195 A61K38/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MCCAFFREY, MARTIN J. ET AL: "Effect of L-arginine infusion of infants with persistent pulmonary hypertension of the newborn." PEDIATRIC RESEARCH, (1994) VOL. 37, NO. 4 PART 2, PP. 341A. MEETING INFO.: 105TH ANNUAL MEETING OF THE AMERICAN PEDIATRIC SOCIETY AND THE 64TH ANNUAL MEETING OF THE SOCIETY FOR PEDIATRIC RESEARCH SAN DIEGO, CALIFORNIA, USA MAY 7-11, 1995 , XP002113470 abstract</p> <p style="text-align: center;">--- -/--</p>	1,2,5-9, 12-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search

30 August 1999

Date of mailing of the international search report

10/09/1999

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INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/IB 99/00413

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BOEGER, R. H. (1) ET AL: "Differential systemic and pulmonary hemodynamic effects of L-arginine in patients with coronary artery disease or primary pulmonary hypertension." INTERNATIONAL JOURNAL OF CLINICAL PHARMACOLOGY AND THERAPEUTICS, (1996) VOL. 34, NO. 8, PP. 323-328. , XP002113471 abstract page 325, column 2 - page 326, column 1, paragraph 1 ---	1,2,5-9, 12-16
X	WEBSTER, J. ET AL: "Elastase-specific inhibitor elafin and endogenous vascular elastase (EVE) in vascular development." FASEB JOURNAL, (1997) VOL. 11, NO. 3, PP. A224. MEETING INFO.: ANNUAL MEETING OF THE PROFESSIONAL RESEARCH SCIENTISTS ON EXPERIMENTAL BIOLOGY 97 NEW ORLEANS, LOUISIANA, USA APRIL 6-9, 1997 , XP002113472 page X ---	1-4, 6-11, 13-16
X	RABINOVITCH, MARLENE: "Elastase and the pathobiology of unexplained pulmonary hypertension" CHEST (1998), 114(3, SUPPL., BRENOT MEMORIAL SYMPOSIUM ON THE PATHOGENESIS OF PRIMARY PULMONARY HYPERTENSION, 1997), 213S-224S , XP002113473 abstract page 213S, column 1 - page 222S, column 2, paragraph 1 ---	1-4, 6-11, 13-16
X	RABINOVITCH, MARLENE: "Elastase and elastase inhibitors and pulmonary and coronary artery disease" INT. CONGR. SER. (1998), 1155(ATHEROSCLEROSIS XI), 317-326 , XP002113474 abstract page 317, paragraph 1 - page 325, paragraph 2 ---	1-4, 6-11, 13-16
X	WO 95 09636 A (UNIV COLUMBIA ;LAWSON CHARLES A (US); PINSKY DAVID J (US); SMERLIN) 13 April 1995 (1995-04-13) abstract; claims 1,49 ---	1,2,5-9, 12-16
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INTERNATIONAL SEARCH REPORT

Int. l. Application No.
PCT/IB 99/00413

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GOSSAGE J R ET AL: "THE NEUTROPHIL ELASTASE INHIBITOR SC-39026 ALTERS THE DEVELOPMENT OF SUSTAINED PULMONARY HYPERTENSION SECONDARY TO CONTINUOUS AIR EMBOLIZATION (CAE)."</p> <p>1991 INTERNATIONAL CONFERENCE OF THE AMERICAN LUNG ASSOCIATION AND THE AMERICAN THORACIC SOCIETY, ANAHEIM, CALIFORNIA, USA, MAY 12-15, 1991. AM REV RESPIR DIS. (1991) 143 (4 PART 2), A187. , XP002113475 abstract</p> <p style="text-align: center;">---</p>	1, 15
X	<p>ADNOT, S. ET AL: "Loss of endothelium-dependent relaxation during chronic hypoxic pulmonary hypertension: Recovery on return to room air or after treatment with L-arginine"</p> <p>BIOL. NITRIC OXIDE, PROC. INT. MEET., 2ND (1992), MEETING DATE 1991, VOLUME 1, 32-4. EDITOR(S): MONCADA, SALVADOR. PUBLISHER: PORTLAND PRESS, LONDON, UK. , XP002113476 page 33, paragraph 3 - page 34, paragraph 3</p> <p style="text-align: center;">---</p>	1, 2, 5-9, 12-16
X	<p>MEHTA S. ET AL: "Short-term pulmonary vasodilation with L-arginine in pulmonary hypertension."</p> <p>CIRCULATION, (1995) 92/6 (1539-1545). , XP002113477 abstract</p> <p style="text-align: center;">---</p>	1, 2, 5-9, 12-16
P, X	<p>WO 98 08500 A (POLI DE FIGUEIREDO LUIZ F ;MATHRU MALI (US); DEWITT DOUGLAS (US);) 5 March 1998 (1998-03-05) abstract page 5, line 5-11; claim 5</p> <p style="text-align: center;">---</p>	1, 2, 5-9, 12-16
E	<p>WO 99 17800 A (AMGEN INC) 15 April 1999 (1999-04-15) abstract page 26, line 8 - page 27, line 8</p> <p style="text-align: center;">---</p>	1, 2, 15, 16
E	<p>US 5 895 788 A (WIDEMAN JR ROBERT F ET AL) 20 April 1999 (1999-04-20) abstract; claims 1-17; tables 1-6</p> <p style="text-align: center;">-----</p>	1, 5-9, 12-16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/00413

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-14
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-14
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3,6-10,13-16 relate to a use defined (inter alia) by reference to the following parameter(s):

P1: inhibitor of (serine) elastase

P2: agent to suppress tenascin

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. A compound is not sufficiently defined by a pharmacological parameter: for clarity of the claims, a structural definition is necessary. A complete search is virtually impossible because it is not exhaustively known which chemical compounds are comprised by the scope of the claims. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to to the general idea underlying the application and to the use of L-arginine and elafin.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 99/00413

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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